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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/606,055	06/25/2003	Charles E. Hart	00-79D1	3796

10117 7590 05/31/2006

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EXAMINER	
BORGEEST, CHRISTINA M	

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 05/31/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/606,055	HART ET AL.	
	Examiner	Art Unit	
	Christina Borgeest	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 March 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 June 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

Claim 25 has been amended in the response filed 30 March 2006. Claims 25-32 are currently under consideration.

The text of those sections of 35 U.S.C. not included in this action can be found in a prior office action mailed 3 January 2006.

Response to Arguments

Applicant's arguments filed 30 March 2006, with respect to the rejection(s) of claim(s) 25-28 and 30-31 under 112, first paragraph for total lack of enablement have been fully considered and are partially persuasive. Particularly, Applicants' declaration under 37 CFR 1.132 provided support for a nexus between mesangial cell proliferation and zvegf4 (also known as PGDF-D). The evidence submitted by Applicant was persuasive for a portion of the claimed subject matter, but not commensurate in scope with the claims. Therefore, the rejection of claims 25-31 under 112, first paragraph, for lack of enablement has been withdrawn in part. The remaining enablement issues are set forth below.

Claims 25-28 and 30-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for administering humanized or human monoclonal antibodies that bind to an epitope of a protein as shown in SEQ ID NO: 2 from amino acid residues 258-370 for the treatment of mesangial proliferative

glomerulonephritis, diabetic nephropathy or lupus nephritis, does not reasonably provide enablement for treatment of all types of kidney fibrosis or glomerulonephritis with antibodies as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." (See In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 Fed. Cir. 1988) These factors include, but are not limited to: (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of one of ordinary skill; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

First claims 25, 28, 30 and 31 recite treatment with an antibody to an epitope of a protein as shown in SEQ ID NO: 2 from amino acid residues 258-370, however, not all types of antibodies are effective in therapy. Booy et al. review the history of antibodies as therapeutics in Arch Immunol. Ther. Exp., 2006, 54, 85-101. Although Booy et al. are writing about cancer therapies, many of the observations made about antibodies can be generalized for treatment of other disorders with antibodies. For instance, early antibody therapeutics, raised in mouse, rabbit or rat generated immune responses in the recipient, leading to quick clearance or even anaphylaxis (see Booy et al., p. 86,

right column, 2nd paragraph). To avoid this problem, humanized antibodies were developed, however, attempts to raise monoclonal antibodies in humans have not been successful for the most part (see p. 94, right column, 3rd paragraph). Hybrid or humanized antibodies diminish immune responses, however, it is thought they would be immunogenic in immunocompetent humans (see p. 95). So generally, only humanized monoclonal antibodies are considered effective for treatment, and claims 25, 28, 30 and 31 encompass polyclonal antibodies and/or those raised in other animals. More specifically, Ostendorf and colleagues show that human monoclonal antibodies are effective in the treatment of mesangioproliferative renal disease (see J Am Soc Nephrol. 2006; 17: 1054-62 and J Am Soc Nephrol. 2003; 14: 2237-47), thus providing support for human or humanized antibody treatment of mesangioproliferative renal disease.

Second, while Applicants have effectively demonstrated a nexus between mesangioproliferative renal disease and zvegf4 overexpression and amelioration with monoclonal antibodies to zvegf4, the terms kidney fibrosis and glomerulonephritis encompass a broad range of diseases with different etiologies. According to Answers.com (accessed 18 May 2006), mesangial proliferative glomerulonephritis is defined as a "type of disease due to deposition of polymerized IgA1 in the mesangium, with a localized proliferation of tissue...and is consistent with IgA nephritis (Berger's disease) and usually presents with macroscopic hematuria", thus is defined as a ***specific type of glomerulonephritis***. However, the more general definition of glomerulonephritis is "primary or secondary autoimmune renal disease...[c]auses are infections (bacterial, vial or parasitic pathogens), autoimmune or paraneoplastic," and

encompasses a much broader range of diseases with many different etiologies than Applicants have shown that mesangioproliferative renal disease can be treated with humanized monoclonal antibodies to amino acid sequences 258 to 370 of SEQ ID NO: 2. Furthermore, according to Bessho et al. (Am J Physiol Renal Physiol. 2003; 284: F1171-F1180), "glomerular mesangial cells proliferation is a key feature of a variety of human glomerular diseases including IgA nephropathy, lupus neprhitis, variants of idiopathic focal sclerosis or amyloid or diabetic nephropathy," (see p. F1171, left column, 1st paragraph). It is the examiner's reasoned belief, based upon evidence in the prior art (Bessho et al., Ostendorf et al. (2003), Ostendorf et al. (2006), Hudkins et al. (J Am Soc Nephrol. 2004; 15: 286-298—see abstract and p. 287, left column, 1st paragraph), Taneda et al. (J Am Soc Nephrol. 2003; 14: 2544-2555—see abstract, and p. 2544, left column, 1st paragraph), and Applicants' arguments and declaration that zvegf4 plays a role in mesangial and tubulointerstitial proliferation, and that such renal injury represents a particular type of injury, but does not encompass all possible types if renal injury. For that reason, zvegf4 antibodies may not necessarily be effective against all types of kidney fibrosis and glomerulonephritis.

Finally, the rejection of claims **29 and 32** under 35 USC 112, 1st paragraph, for enablement is maintained for the reasons given above regarding kidney fibrosis and glomerulonephritis and in the Office action (3 January 2006).

Applicants' argue at p. 3, 3rd and 4th paragraphs that humanized antibodies are well known in the art and have been approved for therapeutic use in the US, which is misplaced since the examiner takes no issue with this statement.

Applicants' argue at p. 4, 1st and 3rd paragraphs that there is a causative link between PGDF-D and glomerular mesangial cell and tubulointerstitial myofibroblast cell proliferation, which is persuasive. What is not persuasive, however, is the extension of the scope to encompass all types of kidney fibrosis and/or glomerulonephritis (as is suggested at p. 4, 2nd paragraph of Applicants' arguments). As stated in the previous remarks under the scope of enablement rejection, it is the examiner's reasoned belief that neither the prior art, nor Applicants have demonstrated that glomerular mesangial cell and tubulointersitial myofibroblast cell proliferation encompass all types of kidney fibrosis and/or glomerulonephritis.

Applicants argue at p. 5, 1st paragraph that the term "reduce kidney fibrosis" indicates at least a statistically significant reduction in disease progression as compared to an untreated patient, which is persuasive. Applicants' also argue that there is no requirement that applicants for patents disclose contraindications for a therapeutic because product safety is the province of the FDA, to which the examiner takes no issue. The issue is that undue experimentation is necessary in cases where Applicants' have not established a nexus between a protein and a disease state. It is the examiner's reasoned belief that neither the prior art, nor Applicants have demonstrated that glomerular mesangial cell and tubulointersitial myofibroblast cell proliferation

encompass all types of kidney fibrosis and/or glomerulonephritis, thus antibodies to zvegf4 could not treat all forms of kidney fibrosis or glomerulonephritis.

Applicants cite the MPEP at p. 5, 2nd paragraph, to which the examiner takes no issue. Applicants further argue that a patent need not disclose what is well known in the art and that enablement is judged in the light of the state of the art, which includes the therapeutic use of monoclonal antibodies, and that Applicants have disclosed sufficient information regarding clinical endpoints, etc. The examiner takes no issue with these statements. The issue, as stated in the previous paragraph is that undue experimentation is necessary in cases where Applicants have not established a nexus between a protein and a disease state. It is the examiner's reasoned belief that neither the prior art, nor Applicants have demonstrated that glomerular mesangial cell and tubulointersitial myofibroblast cell proliferation encompass all types of kidney fibrosis and/or glomerulonephritis, thus antibodies to zvegf4 could not treat all forms of kidney fibrosis or glomerulonephritis.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Borgeest whose telephone number is 571-272-4482. The examiner can normally be reached on 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Elizabeth C. Kemmerer

Christina Borgeest, Ph.D.

ELIZABETH KEMMERER
PRIMARY EXAMINER